Cancer Chemother Pharmacol (1992) 30 (Suppl): S 81–S 84

Cancer Chemotherapy and Pharmacology

Cisplatin-based chemotherapy for the treatment of advanced transitional-cell carcinoma of the urinary tract – a preliminary report*

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Summary. The CMV (cisplatin, methotrexate, and vinblastine) and M-VAC (methotrexate, vinblastine, doxorubicin, and cisplatin) regimens were used to treat 19 patients with advanced transitional-cell carcinoma (TCC) of the urothelial tract. In the CMV group, the partial response rate was 45.5% and the mean response duration was 6.3 months. No complete response was obtained in our series. The median duration of survival was 15.8 and 8.3 months in responders and nonresponders, respectively. The toxic symptoms included one case of sepsis and three cases of renal toxicity. However, nausea and vomiting were experienced by most patients and required the administration of antiemetics. In the M-VAC group, the median duration of survival for responders was longer than that of nonresponders (>10.2 vs 7.2 months), although the number of patients was too small for this difference to reach statistical significance. The toxic symptoms included one case of sepsis, two cases of renal toxicity, and nausea and vomiting in most patients. Bone metastasis in three patients did not respond to chemotherapy (CMV), a finding that is compatible with the results reported by other investigators. In summary, chemotherapy with the CMV or M-VAC regimen was effective in improving the response rate of patients. However, the duration of response was short, toxicity was severe in some cases, and the efficacy against bone lesions was poor. These problems must be solved to improve the outcome of patients with TCC following chemotherapy with the CMV or M-VAC regimens.

Introduction

Transitional-cell carcinoma (TCC) of the urothelial tract is a tumor that responds to chemotherapy [13]. Previously, the options for treatment of local and distant metastatic disease were limited, and the prognosis for such patients was grave. However, the recent management of extensive urothelial cancer has shown much improvement with the development of effective chemotherapeutic agents [14]. During the last decade, many cytotoxic agents have been used in the treatment of patients with metastatic TCC. Single agents such as methotrexate or cisplatin produce a response in approximately 30%–40% of patients, but fewer than 5% survive for 1 year from the time of presentation. Chemotherapeutic programs involving multiple agents have recently become common, and among the most effective combinations are the CMV regimen (cisplatin, methotrexate, and vinblastine) developed by the Stanford Group and the M-VAC regimen (methotrexate, vinblastine, Adriamycin, and cisplatin) pioneered at the Memorial Sloan-Kettering Hospital. The response rates reported for both regimens have been variable, ranging from 56% to 69% [13, 14]. This report documents our experience with the use of cisplatin-based therapy involving CMV or M-VAC in treating metastatic TCC.

Patients and methods

From February 1989 to February 1990, 19 patients with pathologically proven metastatic TCC of the urothelial tract were randomly included in this study. There were 18 men and 1 women aged a mean of 58 years (range, 31–78 years). All 19 patients had distant metastases, which involved the pelvic lymph nodes in 9 cases, the liver in 2, bone in 3, the lung in 2, and the retroperitoneal lymph nodes in 6. The primary sites were the urinary bladder in 15 patients and the upper urinary tract in 4.

CMV group. A total of 11 patients were treated with the CMV regimen. On day 1, 4 mg/m^2 vinblastine and 30 mg/m^2 methotrexate were given intravenously, followed by 100 mg/m^2 cisplatin 24 h later. On day 8, the doses of methotrexate and vinblastine were repeated. This course was

* Presented at the 4th International Conference on Treatment of Urinary Tract Tumors with Adriamycin/Farmorubicin, 16-17 November 1990, Osaka, Japan

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Table 1. CMV group: response and duration of survival

Patient	Age (years) sex (M/F)	Cycle(s)	Follow-up (months)	Response/ duration (months)	Metastatic site
1	60/F	9	16 (dead)	PR/10	Retroperitoneal node
2	76/M	6	8 (dead)	PD/5	Liver, bone
3	71/M	4	18 (dead)	PR/7	Retroperitoneal node
4	72/M	4	20 (dead)	PR/4	Pelvic node, rectum
5	76/M	3	16 (dead)	PD	Pelvic node
6	34/M	3	12 (dead)	PR/6	Pelvic node
7	64/M	2	8 (dead)	PD	Pelvic node
8	37/M	3	8 (dead)	PD	Bone
9	63/M	7	13 (dead)	PR/6	Pelvic node
10	65/M	3	3 (dead)	PD	Lung, retroperitoneal node
11	35/M	2	7 (dead)	PD	Bone

Median survival: responders, 15.8 months; nonresponders, 8.3 months; PR rate, 45%; Mean response duration, 6.3 months

repeated every 3 weeks until the patients either no longer tolerated it or showed a response.

M-VAC group. Eight patients were treated with the M-VAC regimen. On day 1, 30 mg/m^2 methotrexate was given intravenously by drip infusion, followed by the administration of 3 mg/m^2 vinblastine, 30 mg/m^2 Adriamycin, and 70 mg/m^2 cisplatin 24 h later. The course concluded with the administration of 30 mg/m^2 methotrexate and 3 mg/m^2 vinblastine on days 15 and 22. This course was repeated in a 4-week cycle. The clinical evaluation included a physical examination, chest X-rays, cystoscopy, computed tomography, and bone and liver scans.

Evaluation of response. A complete response (CR) was defined as the disappearance of all evidence of disease as assessed by physical, biochemical, and radiographical examinations. A partial response (PR) represented a decrease of $\geq$50% in the abnormally elevated parameters directly related to the tumor and the absence of any new lesions. Progressive disease (PD) consisted of an increase of $\geq$25% in the measurable lesion or the appearance of a new lesion. The duration of the response was measured from the time at which a CR or PR was first noted.

Results

CMV group

Of 11 evaluable patients, 5 (45%) achieved a PR during CMV chemotherapy (Table 1). No CR was obtained in this group. There were six nonresponders, including one whose condition remained stable and five cases of PD. The median age of the partial responders and nonresponders was 60 and 58.8 years, respectively. PRs were noted mostly in the retroperitoneal lymph node and the pelvic lymph node. No response was observed in bone, hepatic, or pulmonary metastatic lesions. The median survival of the PR group was 15.8 months in contrast to the 8.3 months noted for the nonresponders. The mean duration of response was 6.3 months. All of the patients experienced nausea and vomiting. Three patients showed evidence of CMV-related nephrotoxicity as defined by a decrease in creatinine clearance (C_{Cr}) or a rise in serum creatinine amounting to >2.0 mg/100 ml following any treatment cycle. Two patients developed anemia [hemoglobin (Hb), <10 mg/dl] due to persistent gross hematuria. Two subjects developed leukopenia, which resulted in sepsis in one case (Table 2). No toxicity-related death occurred.

M-VAC group

In all 4 of 8 patients (50%) achieved a PR in response to M-VAC (Table 3). No CR was obtained in this group either. The median age of the partial responders and nonresponders was 57.3 and 54.3 years, respectively. PRs were noted mostly in cases of pelvic and retroperitoneal lymph-node lesions. Patient 6 showed involvement of the retroperitoneal lymph nodes and lung but achieved a PR for 5 months. The median survival of the partial responders was 10.2+ months as compared with the 7.2 months noted for the nonresponders. The mean duration of response was 5.2 months. Nausea and vomiting was experienced by all of the patients. Two subjects showed evidence of M-VAC-related nephrotoxicity as defined by a decrease in Ccr or a rise in serum creatinine amounting to >2.0 mg/100 ml fol-

Table 2. CMV toxicity

Patient	Hb, <10 mg/dl	WBC, <1,000/mm^3	Platelet count, <100,000/mm^3	C_{Cr} (1st/last)	N/V	Other problems
1	–	–	–	58/58	+++	
2	–	–	–	115/80	++	
3	–	+	–	52/16	++	
4	–	–	–	60/17	++	
5	+HU	–	–	80/80	++	
6	–	–	–	1.2/8.2 (Cr)	++	NIDDM
7	+HU	–	–	80/70	++	
8	–	+	+	47/30	+++	Sepsis
9	–	–	–	75/60	++	
10	–	–	–	80/75	++	
11	–	–	–	96/63.8	+	

HU, Hematuria; N/V, nausea/vomiting; Cr, creatinine; NIDDM, Non-Insulin Dependent Diabetes Mellitus

Table 3. M-VAC group: response and duration of survival

Patient	Age (years) sex (M/F)	Cycle(s)	Follow-up (months)	Response/duration (months)	Metastatic site
1	67/M	2	7 (dead)	PD	Pelvic node
2	70/M	6	10 (alive)	PR/6	Pelvic node
3	64/M	6	11 (alive)	PR/6	Pelvic node
4	31/M	3	8 (alive)	PR/4	Pelvic node
5	78/M	3	7 (dead)	PD	Liver, retroperitoneal node
6	64/M	4	12 (alive)	PR/5	Lung, retroperitoneal node
7	38/M	5	9 (dead)	PD	Retroperitoneal node
8	34/M	5	6 (dead)	PD	Rectum

Median survival: responders, >10.2 months; nonresponders, 7.2 months; PR rate, 50%; Mean response duration, 5.2 months

Table 4. M-VAC toxicity

Patient	Hb, <10 mg/dl	WBC, <1,000/mm^3	Platelet count, <100,000/mm^3	C_{Cr} (1st/last)	N/V	Other problems
1	–	–	–	78/75	++	
2	+HU	–	–	76/15	++	
3	–	+	+	60/55	++	
4	–	+	–	67/15	+++	Sepsis
5	+HU	–	–	70/60	+	
6	–	–	–	65/60	++	
7	–	–	–	80/75	+	
8	–	–	–	80/65	++	

HU, Hematuria; N/V, nausea/vomiting

lowing any treatment cycle. Two patients developed anemia due to persistent gross hematuria. Two subjects developed leukopenia, which resulted in sepsis in one case. However, no sepsis-related death was recorded (Table 4).

Discussion

In several studies, investigators have obtained favorable results using combination chemotherapy involving various regimens in patients with advanced TCC of the urothelial tract [9, 13, 14]. On the other hand, clinical and postmortem data show that micrometastases are often present at the initial diagnosis [5]. In view of the observation that most patients presenting with high-grade, high-stage bladder cancer have systemic rather than local disease, a significant improvement in survival requires effective systemic therapy [12]. Historically, patients with metastatic carcinoma of the bladder survive for a median of 3 months from the time of detection of metastatic disease [1]. This high mortality demonstrates the need for more effective therapy.

Among the cytotoxic agents, cisplatin (CDDP), Adriamycin (ADR), methotrexate (MTX), 5-fluorouracil (5-FU), and cyclophosphamide (CTX) have thus far proved to be effective, exhibiting significant clinical activity [3, 4, 10, 16]. Of these, cisplatin has been considered to be the most promising agent since the first report of a 35% PR rate by Yogoda et al. [18]. Other workers have since reported response rates ranging from 20% to 43% [7, 17].

Therapeutic synergism has been described for combinations of various regimens [9, 13, 14]. In clinical studies, the combination of cisplatin, cyclophosphamide, and doxorubicin (CAP) has produced response rates ranging from 38% to 46% [11, 15]. However, a low response rate of 13% has been reported, and this suggests that the response rate obtained using the CAP regimen may not be superior to that obtained using a single agent such as cisplatin [2]. On the other hand, M-VAC combination chemotherapy has resulted in an overall response rate of 69%, including a CR rate of 37%, in patients with advanced TCC [14]. The CMV regimen has produced an overall response rate of 56%, including a CR rate of 28%. The median survival of complete responders has been 11 months vs 7 months for partial responders and 6 months for nonresponders [6].

The present results, including 5 PRs (45%) to the CMV regimen and 4 PRs (50%) to the M-VAC regimen, demonstrate that cisplatin-based combination chemotherapy exerts substantial antitumor activity in patients with advanced TCC of the urinary tract. Partial tumor regression was more frequently observed in retroperitoneal lymph-node lesions. No response was noted in metastatic bone or liver lesions; this finding is compatible with a previous report of the lack of a response by such lesions to conventional chemotherapy [8]. No brain metastasis was detected in our patients. However, other investigators have reported a 12% incidence of brain metastases in patients with TCC [14]. Because of their poor prognosis, brain lesions should be examined by computed tomography in cases of distant metastasis [8]. The five patients who responded partially to CMV therapy experienced prolonged survival as compared with the nonresponders (15.8 vs 8.3 months). On average, the partial responders in the M-VAC group survived for longer than 10.2 months, which was better than the 7.2 months noted for the nonresponders. The mean dura-

tion of response was 5.2 months. Although no CR was obtained in our series of patients, the median duration of survival for the partial responders was longer than the values previously obtained by other workers using the M-VAC and CMV regimens [6, 8, 14]. Herr [7] reported that the duration of survival observed for both responders and nonresponders was longer than that noted for untreated patients [7].

Although the immediate efficacy of CMV and M-VAC therapy was satisfactory as judged by the overall response rates of 45% and 50%, respectively, the mean duration of response was 6.3 and 5.2 months, respectively, which was conversely short. Other investigators have reported mean durations of response of about 10.1 and 6.2 months for complete and partial responders, respectively [8]. No age difference was observed between partial responders and nonresponders receiving either the CMV or the M-VAC regimen.

The toxicity of both regimens was significant, with the most prominent side effect being nausea and vomiting. Fortunately, these symptoms improved in most cases following antiemetic treatment. No toxicity-related death occurred. Five patients (three receiving CMV and two receiving M-VAC) developed nephrotoxicity, which resulted in modification of the treatment doses. Since February 1990, we have modified the regimen of M-VAC to M-VACarbo (whereby carboplatin is substituted for cisplatin), the rationale being that carboplatin has less emetic activity and produces less renal toxicity, which would make its use safe in patients with impaired renal function. The results obtained using M-VACarbo will be presented in the future.

Although cisplatin-based chemotherapy (M-VAC or CMV) yields high response rates, the duration of response is short, the toxicity is severe, and the effectiveness against bone lesions is poor. These problems must be solved to improve the prognosis for patients with advanced urothelial cancer.

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